INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003588

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-10	as originally filed
Claims, Numbers	
1-7	received on 23.03.2005 with letter of 18.03.2005
Drawings, Sheets	
1/2, 2/2	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-7
	No:	Claims	1-4
Inventive step (IS)	Yes:	Claims	5-7
	No:	Claims	1-4
Industrial applicability (IA)	Yes:	Claims	1-7
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V.

The following documents are referred to in this communication:

D1 : VAN DEN BERG, C. J. ET AL: "Inositol phosphates and phytic acid as inhibitors of biological calcification in the rat" CLINICAL SCIENCE , 43(3), 377-83 CODEN: CSCIAE; ISSN: 0143-5221, 1972, XP008042000

D2: GRASES, F. ET AL: "Phytate prevents tissue calcifications in female rats" BIOFACTORS , 11(3), 171-177 CODEN: BIFAEU; ISSN: 0951-6433, 2000, XP008041991

D3: GRASES, F. ET AL: "Effects of phytic acid on renal stone formation in rats" SCANDINAVIAN JOURNAL OF UROLOGY AND NEPHROLOGY , 32(4), 261-265 CODEN: SJUNAS; ISSN: 0036-5599, 1998, XP008041988

D4 : KASTING G B ET AL: "SKIN PENETRATION ENHANCEMENT METHODS FOR HYDROPHILIC COMPOUNDS" PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 14, no. 11, SUPPL, November 1997 (1997-11), page S452, XP001105174 ISSN: 0724-8741

D5 : US 5 268 176 A (ZNAIDEN ET AL) 7 December 1993 (1993-12-07)

D6 : US 5 082 833 A (SHAMSUDDIN ET AL) 21 January 1992 (1992-01-21)

1. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4 is not new in the sense of Article 33(2) PCT.
Document D1 discloses phytic acid (myo-inositol hexaphosphate) as an inhibitor of biological calcification. Phytic acid when injected parenterally (subcutaneously) prevented aortic calcification in rats. The injectable composition used in D1 is suitable for topical administration and therefore "adapted to topical administration".

2. However, the subject-matter of the present application as far as it relates to the use of myo-inositol for the manufacture of a formulation for the treatment and/or prevention **by topical administration** of a disease associated with the development of heterogenous

nucleants which induce the development of pathological calcification in a soft tissue appears to be new and inventive.

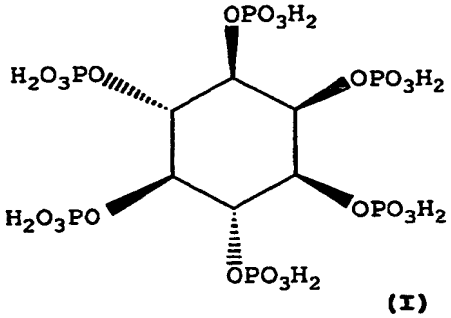
2.1 Novelty in sense of Article 33(2) PCT is acknowledged since no documents of the prior art disclose the use of myo-inositol hexaphosphate for treating soft tissue calcification by topical administration.

2.2 In the light of the prior art, the problem to be solved by the present application is to provide an alternative way of administering myo-inositol hexaphosphate which improves the bioavailability of said compound in order to treat of prevent the formation of calcifications in soft tissue.
No indications were found that would have led the skilled person to choose the topical administration in order to solve the problem posed, so an inventive step in the sense of article 33(3) PCT is acknowledge.
Documents D4-D5 disclose topical formulation of phytate but do not mention or suggest that said phytate is capable of being absorbed through the skin, passing into the bloodstream and acting on pathological calcifications.
Furthermore, the applicant provided some experimental data showing that the bioavailability of phytate when it is applied on the skin in order to treat soft calcifications is surprisingly higher than the one achieved by oral administration. Such an improved bioavailability by topical administration could not have been predicted from the prior art.

ENCLOSURE-1

NEW SET OF AMENDED CLAIMS

1. Use of a composition including myo-inositol hexaphosphate corresponding to the formula:



(I)

or pharmaceutically acceptable salts thereof in a form adapted to topical administration for the manufacture of a formulation for the prevention and/or treatment of a disease associated with the development of heterogeneous nucleants which induce the development of pathological calcification in a soft tissue.

2. Use according to claim 1 wherein the disease is associated with the development of calcifications in a soft tissue.

3. Use according to Claim 1, in which said disease consists on a subepithelial dystrophic calcification.

4. Use according to Claim 1, in which said disease consists on an arterial calcification.

5. Use according to Claim 1, in which said disease consists on a renal calcification.

6. Use according to Claim 1, in which said disease consists on a cerebral calcification.

7. Use according to Claim 1, in which said disease consists on a pulmonary calcification.